Remarks

I. Status of the Claims and Support for the Amendments

Claims 1, 3-7, 9-21, 23, 24, 35, 38, 59, 61-63, 65, 67, 73-77, 79, 90, 94, 109-131, 134 and 137 have been amended herein.

Claims 8, 25, 26, 36, 37, 60, 64, 66, 68-72, 80, 81, 91, 92, 93, 95, 96, 132, 133, 135, 136, 138 and 139 have been canceled herein without prejudice to or disclaimer of the subject matter therein.

New claims 140-171 have been added.

The subject matter of claim 59 has been divided into claim 59, as amended, and into new claim 146. The new claims that depend from claim 146 correspond to claims that depend from claim 59.

Support for the amendment of claims 1, 3-7, 9-21, 23, 24, 35, 38, 59, 61-63, 65, 67, 73-77, 79, 90, 94, 109-131, 134 and 137 and for new claims 140-171 is found in the present Specification, for example at page 10, paragraph [0024]; and page 18, paragraph [0053]; pages 59-61 (claim 146); and pages 62-64 (claim 59).

No new matter has been added by this amendment.

II. Statement Of The Substance Of The Examiner Interview

On October 19, 2010, the undersigned met with Examiner Gupta. Those present at the interview also included Dr. Merry Sherman, Dr. Mark Saifer and Applicants' attorney Dr. Eldora Ellison. During the interview, Applicants discussed the outstanding rejections in the Office Action. Applicants and the undersigned thank Examiner Gupta for the frank and courteous discussion.

III. The Information Disclosure Statement

At page 2 of the Office Action, the Examiner explained that certain foreign language documents had not been considered. The documents to which the Examiner referred are being refiled with an information disclosure statement filed herewith. For each of the foreign language documents listed in the information disclosure statement, either (a) a concise statement of relevance is provided, or (b) the foreign language document is a translation of a corresponding English language document that is either of record or is being made of record, such that the requirement for a concise statement of relevance is satisfied by the translation. *See* M.P.E.P. § 609.04(a)III.

Applicants submit that a concise statement of the relevance of each foreign language document has been provided. Applicants respectfully request that the Examiner indicate in the record that the foreign language documents cited in the information disclosure statement filed herewith have been considered.

IV. The Status Of Claims 112, 115-117, 120 And 123-125

At page 2 of the Office Action, the Examiner stated that claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-111, 113, 114, 118, 119, 121, 122 and 126-133 have been examined. According to the "Disposition of the Claims" at page 1 of the Office Action, claims 36, 37, 91, 92, 112, 115-117, 120, 123-125 have been withdrawn from consideration. Claims 36, 37, 91, 92, 135, 136, 138 and 139 have been canceled herein. Applicants submit that claims 112, 115-117, 120 and 123-125 should be examined.

V. The Novelty Rejection Over Lee Should Be Withdrawn

At page 3 of the Office Action, the Examiner rejected claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-111, 118 and 119 under 35 U.S.C. § 102(b) as allegedly

anticipated by Lee *et al.*, U.S. Patent No. 4,261,973 (hereinafter "Lee"). Applicants respectfully traverse this rejection. Lee fails to anticipate the claimed invention.

Claims 8, 25, 26, 60, 64, 66, 68-72, 80, 81, 93, 95 and 96 have been canceled. With respect to the remaining rejected claims, Applicants provide the following comments.

As amended herein, claim 1 of the present application recites:

> 1. A composition comprising a conjugate comprising a peptide, protein or glycoprotein covalently attached to at least one linear or branched polyalkylene glycol(s),
>
> wherein *at least 95%* of said polyalkylene glycol(s) is or are attached to said peptide, protein or glycoprotein at a single site on said polyalkylene glycol(s),
>
> wherein a hydroxyl group is present on *at least 95% of the distal polyalkylene glycol termini in said conjugate*, and
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> wherein said conjugate in said composition exhibits reduced antigenicity compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in said conjugate.

(Emphases added.)

Hence, claim 1 recites that:

(a) at least 95% of the polyalkylene glycol(s) is (or are) is attached to the peptide, protein or glycoprotein at a single site on the polyalkylene glycol(s), and

(b) a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

Lee fails to teach each of those limitations of claim 1.

At page 3 of the Office Action, the Examiner stated that "the reference [Lee] does not teach that the peg [sic] group is methoxylated and thus it would have a distal

hydroxyl group at the distal end." Applicants respectfully disagree. Lee discloses polyethylene glycol ("PEG") at column 4, line 66 to column 5, line 4. The PEG molecules utilized in Examples 1 and 2 of Lee are PEG diols. *See* the Saifer Declaration at paragraph 4. At column 5, line 2, Lee discloses that cyanuric chloride was used as the coupling agent to couple PEG either to ovalbumin or to ragweed antigen. *See id.*

In view of the disclosures in Lee, one of ordinary skill in the art would have understood that *less than* 95% of the PEG diol disclosed in Lee would have been activated at *only* one end. *See* the Saifer Declaration at paragraph 5. Thus, one of ordinary skill in the art would have understood that *less than 95%* of the polyalkylene glycol(s) disclosed in Lee would have been attached to ovalbumin or to ragweed antigen at a *single* site on the polyalkylene glycol(s).

A person of ordinary skill in the art would have had such an understanding because of the binomial statistics of end-group activation of diols. As explained in Dr. Saifer's Declaration, the binomial statistics of end-group activation prevent more than 50% of the PEG diol from becoming monofunctionally activated during an activation reaction that involves PEG diol, such as the reaction disclosed in Lee. When the maximum of 50% monoactivation is reached, 25% of the PEG diols would be *bis*-activated, and 25% of the PEG diols would remain unactivated. *See id.* As one increases the extent of activation further, the fraction of PEG diols that is *bis*-activated would increase to more than 50%, but the fraction of monoactivated PEG *decreases*, as does the fraction of unactivated PEG. *See id.* These binomial statistics are illustrated quantitatively in McManus *et al.*, EP 1 656 410 B1 (hereinafter "McManus," a copy of which is attached to the Saifer Declaration as Exhibit B). McManus discusses such

statistics at page 5 (paragraph [0028]) and page 9 [paragraph [0077]), and in Figure 1. *See* the Saifer Declaration at paragraph 5. The binomial statistics of diol activation that are illustrated in McManus have long been known. *See id.*

Accordingly, Lee does not disclose or suggest compositions in which *at least 95%* of the polyalkylene glycols are attached to a peptide, protein or glycoprotein at a *single* site on the polyalkylene glycol, as recited in the present claims. For example, Lee does not disclose capping one end of the PEG diols in order to prevent activation of both ends of the PEG. *See* the Saifer Declaration at paragraph 5. Lee also does not disclose purifying PEG that is activated at only one end prior to coupling the PEG to ovalbumin or ragweed antigen. *See id.*

Even if the activation reaction in Lee were permitted to proceed past the maximum of 50% monoactivation, Lee would not have arrived at the presently-claimed compositions. Allowing such reactions to proceed results in activating both ends of the PEG diols in Lee, which would have resulted in intramolecular or intermolecular cross-linking of PEG to ovalbumin or to ragweed antigen. That is, *both ends* of the activated PEG would have bound covalently to one or two molecules of ovalbumin or to one or two molecules of ragweed antigen, respectively. *See* the Saifer Declaration at paragraph 6. Such compositions are not compositions in which *at least 95%* of the polyalkylene glycols are attached to a peptide, protein or glycoprotein at a *single* site on the polyalkylene glycol, as recited in the present claims.

Thus, the PEG diols and the activation method used in Lee would have resulted in *less* than 95% of the PEG diol being activated at only one end, and thus Lee does *not* disclose the claimed composition in which *at least 95%* of the polyalkylene glycol is

attached to the peptide, protein or glycoprotein *at a single site* on the polyalkylene glycol.

The PEG molecules utilized in Example 3 of Lee (starting at column 15, line 1) also would not have anticipated the present claims. The PEG molecules in Lee's Example 3 are *methoxy*poly(ethylene glycols) or *m*PEGs, the single terminal hydroxyl group of which was activated to permit coupling to dog serum albumin. Such conjugates would have *methoxyl* groups, not *hydroxyl* groups, at the distal termini of the coupled PEG. *See* the Saifer Declaration at paragraph 7. Thus, such conjugates are not compositions wherein a hydroxyl group is present on *at least 95% of the distal polyalkylene glycol termini in said conjugate*, as recited in the present claims. Therefore, for at least these reasons, Lee fails to teach a composition in which: (i) at least 95% of the polyalkylene glycol(s) is attached to the peptide, protein or glycoprotein at a single site on the polyalkylene glycol(s), and (ii) a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate. *See* the Saifer Declaration at paragraph 8.

For at least the reasons discussed above, Lee fails to anticipate the claimed invention. Applicants respectfully request that this rejection be reconsidered and withdrawn.

VI. The Lack Of Novelty Rejection Over Pepinsky Should Be Withdrawn

A. The Rejection

At page 4 of the Office Action, the Examiner rejected claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109, 110, 114, 118 and 122 under 35 U.S.C. § 102(b) as allegedly anticipated by Pepinsky *et al.*, WO 00/23114 (hereinafter "Pepinsky").

Applicants respectfully traverse this rejection. Pepinsky fails to anticipate the claimed invention.

Claims 8, 25, 26, 60, 64, 66, 68-72, 80, 81, 93, 95 and 96 have been canceled. With respect to the remaining rejected claims, Applicants provide the following comments.

B. In View Of Its Breadth, The Term "Polymer" Does Not Anticipate The Specific Type Of Polymer (A Hydroxy-Terminated Polyalkylene Glycol) Set Forth In The Present Claims

The disclosure of a broad genus in a document does not anticipate a claimed species, unless the document narrows the broadly disclosed genus by setting forth a *specific preference* for a narrower reading of the broad genus. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008); and *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006).

Pepinsky's broad disclosure fails to teach the claimed invention. At page 19, line 13, Pepinsky refers generically to a "polymer." However, independent claim 1 of the present application recites that a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

As the Examiner stated at page 4 of the Office Action, Pepinsky discloses that "numerous polymers can be used," and polyalkylene glycols are only one type of the "numerous" types of polymers encompassed by the term "polymers" in Pepinsky. Evidence for this is found in Pepinsky, which states that polyalkylene oxide (a type of polyalkylene glycol[1]) is just one example of the types of polymers that can be used.

[1] PEG is a type of polyalkylene glycol. At page 21, line 19, Pepinsky stated that PEG is one example of a polyalkylene oxide.

> *As an* ***alternative*** *to polyalkylene oxides* dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like may be used. Those of ordinary skill in the art will recognize that the foregoing list is merely illustrative and that *all polymer materials having the qualities described herein are contemplated.*

Pepinsky at page 21, line 27 to page 22, line 2 (emphases added).

Furthermore, a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate is an even more particular type of conjugate than is encompassed by the conjugate made using the broad kind of "polymer" in Pepinsky.

Pepinsky's disclosure of the broad genus of "polymers" does not anticipate the particular type of polymer (hydroxyl-terminated polyalkylene glycol) recited in the claimed invention, because Pepinsky does not set forth a preference for a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

Pepinsky discusses polyalkylene glycols at page 3, lines 16-22; page 4, lines 1-6; page 20, lines 12, 20 and 28; page 21, lines 8-27; page 22, lines 7-13; page 23, line 7; page 44, line 3; and pages 43-57 (the Examples). However, those portions of Pepinsky do not exclude *alkoxy* polyalkylene glycols, which if linear, have an *alkoxyl* group (not a hydroxyl group) at the distal terminus (not a hydroxyl group) or, if branched, have an *alkoxyl* group (not a hydroxyl group) at distal termini (not a hydroxyl group).

At page 18 lines 13-14, Pepinsky stated that "[i]llustrative polymers that may usefully be employed to achieve these desirable characteristics are described herein below in exemplary reaction schemes." Hence, Pepinsky referred one of ordinary skill in

the art to the Examples. For example, in Example 2 (at page 44, line 7), Pepinsky employed a 20 kDa PEG [polyethylene glycol] *aldehyde* to make a conjugate with interferon-beta-1a. Pepinsky also stated:

> In the practice of the present invention, polyalkylene glycol residues of C1-C4 *alkyl* polyalkylene glycols, preferably polyethylene glycol (PEG), or poly(oxy)alkylene glycol residues of such glycols are advantageously incorporated in the polymer systems of interest.

Pepinsky at page 21, lines 13-16.

Hence, Pepinsky discloses that an *alkyl* polyethylene glycol could be used, but does not disclose a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

However, Pepinsky's references to polyalkylene glycols do not constitute a "preference" for polyalkylene glycols over other types of polymers, because Pepinsky stated clearly that there are *alternatives* to polyalkylene glycols. *See* Pepinsky at page 21, line 27 to page 22, line 2.

Hence, Pepinsky's teaching that "all polymer materials having the qualities described herein are contemplated" means that Pepinsky did *not* set forth a preference for a polyalkylene glycol, from among the broad genus of "polymers," much less set forth a preference for a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

In accordance with *Sanofi-Synthelabo* and *Eli Lilly*, Pepinsky fails to teach the conjugate recited in independent claim 1. Therefore, for at least this reason, Pepinsky fails to anticipate independent claim 1 and the rejected dependent claims.

C. The Examiner's Interpretation Of Pepinsky Is, Respectfully, Incorrect

The Examiner stated:

> Pepinsky et al. teaches modification of interferon with a polymer (see page 17). The reference states that the polymer utilized contains at least one terminal hydroxyl group (see page 19). . . . The reference teaches *numerous polymers* can be used such as PEG . . . .

Office Action at page 4 (emphasis added).

At page 19, Pepinsky provided a discussion of the reaction between a polymer and interferon-*beta*-1a. Pepinsky stated:

> The reactions may take place by any suitable method used for reacting biologically active materials with inert polymers, preferably at about pH 5-7 if the reactive groups are on the alpha amino group at the N-terminus. Generally the process involves *preparing an activated polymer (that may have at least one terminal hydroxyl group)* and thereafter reacting the protein with *the activated polymer* to produce the soluble protein suitable for formulation. The above modification reaction can be performed by several methods, which may involve one or more steps.

Pepinsky at page 19, lines 10-16 (emphases added).

At the Examiner interview on October 19, 2010, the Examiner's stated basis for the rejection over Pepinsky was discussed. It is Applicants' understanding that the Examiner interprets Pepinsky's statement that the polymer "may have at least one terminal hydroxyl group" as referring to the status of the polymer *after* activation of the polymer.

Under the Examiner's interpretation of Pepinsky, after the polymer is activated, the polymer contains at least one terminal hydroxyl group, and after the activated polymer is coupled to interferon-*beta*-1a, the polymer *still* contains at least one terminal

hydroxyl group.

Applicants respectfully disagree with the Examiner's interpretation. As the Examiner acknowledged at the interview, Pepinsky's disclosure of "polymers" is quite broad. The broad genus of polymers disclosed in Pepinsky fails to anticipate the polyalkylene glycol recited in the present claims.

Indeed, Pepinsky included polyols, such as dextrans and other carbohydrates, among the polymers said to be suitable for coupling to interferon-*beta*-1a. Since polyols, such as dextrans and other carbohydrates, can have many hydroxyl groups (only some of which may be terminal hydroxyl groups), Pepinsky's use of the term "polymers" cannot properly be interpreted as synonymous with the polyalkylene glycols used to make the conjugate of the present invention, in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate. *See* the Saifer Declaration at paragraph 10.

Applicants respectfully disagree with the Examiner's interpretation of the disclosure at page 19, line 13 of Pepinsky. Even if the "activated polymer" to which Pepinsky referred at page 19, line 13 were a polyalkylene glycol, and Applicants do not concede that it was, it would be one in which a terminal hydroxyl group is *not* present on the polymer after the polymer has been attached to interferon-*beta*-1a. Thus, even if Pepinsky disclosed a conjugate comprising a polyalkylene glycol attached to interferon-*beta*-1a, the polyalkylene glycol lacks a hydroxyl group at its distal terminus (or termini). Evidence in support of this interpretation is found in Pepinsky:

> The interferon-beta-la is conjugated most preferably *via a terminal reactive group* on the polymer although conjugations can also be branched from the non-terminal

> reactive groups. *The polymer with the reactive group(s) is designated herein as "activated polymer".* The reactive group selectively reacts with free amino or other reactive groups on the protein.

Pepinsky at page 18, lines 17-21 (emphases added).

One of ordinary skill in the art would have understood from Pepinsky at page 18, lines 17-21 that, even if the polymer discussed at page 19, line 13 of Pepinsky has a *single* terminal hydroxyl group, it is that terminal hydroxyl group on the polymer that is "activated." *See* the Saifer Declaration at paragraph 11. As a result, the activated polymer discussed at page 19 of Pepinsky could not have contained both a single group that is reactive with proteins *and* a terminal hydroxyl group following activation of the polymer. *See id.* Similarly, the polymer would not have contained a terminal hydroxyl group after the polymer was attached to a single interferon-*beta*-1a at a single site on the polymer, since any of Pepinsky's polymers that has multiple hydroxyl groups would have been made reactive at many hydroxyl groups, if not at every hydroxyl group.

Therefore, Pepinsky fails to teach a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

For at least the reasons discussed above, Pepinsky fails to teach the composition of independent claim 1 and the rejected dependent claims.

D. Pepinsky Fails To Anticipate Claims 18, 19, 74, 75, 94-96, 140 And 141

Claims 95 and 96 have been canceled. Claims 18 and 74 recite that the peptide, protein or glycoprotein is covalently attached to from one to about five molecules of the polyalkylene glycol. Claims 19 and 75 recite that the peptide, protein or glycoprotein is covalently attached to one or two molecules of the polyalkylene glycol. Claims 140 and

141 recite that the peptide, protein or glycoprotein is covalently attached to from one to three strands of the polyalkylene glycol. Claim 94 recites a kit that comprises more than one container comprising the composition of claim 1.

Claims 18, 19, 74, 75, 94, 140 and 141 depend ultimately from claim 1. For the same reasons that Pepinsky fails to teach the composition of claim 1, Pepinsky fails to teach the composition of claims 18, 19, 74, 75, 140, and 141, and the kit of claim 94.

E. Summary

Pepinsky fails to anticipate the claimed invention. Applicants respectfully request that this rejection be reconsidered and withdrawn.

VII. The Obviousness Rejection Over Delgado, Zalipsky And Pepinsky Should Be Withdrawn

A. The Rejection

At page 6 of the Office Action, the Examiner rejected claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109, 110, 113, 118, 121 and 126-133 under 35 U.S.C. § 103(a) as allegedly obvious over Delgado *et al.*, U.S. Patent No. 5,349,052 (hereinafter "Delgado") in view of Zalipsky *et al.*, "*Eur. Polym. J. 19*: 1177-1183 (1983) (hereinafter "Zalipsky")[2] and Pepinsky. Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established.

Claims 8, 25, 26, 60, 64, 66, 68-72, 80, 81, 93, 95, 96, 132 and 133 have been canceled. With respect to the remaining rejected claims, Applicants provide the following remarks.

[2]Applicants and the undersigned thank the Examiner for confirming the Zalipsky citation to the undersigned via telephone on October 6, 2010.

The Examiner stated:

> Delgado et al. teaches pegylated GM-CSF (see abstract)… The difference between the prior art and the instant application is that the reference utilizes mPEG rather than a PEG with a distal hydroxyl group.
>
> However, Zalipsky et al. teaches that PEG groups can be attached to increase half life (see page 1177). The reference states in order to make possible the attachment of drugs having other functional groups such as amino or hydroxyl, there was a need to preparing [sic] PEG having other functional end groups. The reference specifically teaches pegylation using PEG-COOH which [sic] conjugated to the active agent through amide bonds (see page 1181). *Note that the use of such a PEG would contain a distal OH on the PEG.*
>
> Pepinsky et al. teaches modification of interferon with a polymer (see page 17). The reference states that the polymer utilized contains at least one terminal hydroxyl group (see page 19). The reference specifically teaches the reaction of PEG-aldehyde with interferon (see page 19-20). The reference teaches numerous polymers can be used such as PEG . . . .
>
> It would have been obvious to pegylated [sic] the GM-CSF using either PEG-COOH or PEG-aldehyde because such PEG groups have been utilized in the art to pegylate therapeutic molecules. There would have been a reasonable expectation of success because such both [sic] PEG-COOH or PEG-aldehyde would allow for conjugation of PEG to a [sic] amine for the formation of an amide bond.

Office Action at pages 6-8 (emphasis added).

A. A Prima Facie Case Of Obviousness Has Not Been Established

Applicants respectfully disagree with the Examiner's analysis. In order for an obviousness rejection to be proper, it is necessary for the Examiner to identify reasons why one of ordinary skill in the art would have combined the cited art in an effort to obtain the claimed invention. *See KSR International Co. v. Teleflex, Inc.*, 127 S. Ct.

1727, 1741 (2007) ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."). Here, the Examiner has not provided adequate reasons why one of ordinary skill in the art would have combined Delgado, Zalipsky and Pepinsky in an effort to obtain the claimed invention.

In fact, one of ordinary skill in the art would *not* have combined Delgado, Zalipsky and Pepinsky to obtain the claimed conjugate. Even in combination, Delgado, Zalipsky and Pepinsky would not have provided the claimed invention, at least because even in combination, Delgado, Zalipsky and Pepinsky would not have provided:

(a) at least 95% of the polyalkylene glycol(s) is (or are) attached to the peptide, protein or

glycoprotein at a single site on the polyalkylene glycol(s), and,

(b) that a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate, and

(c) that wherein the conjugate in the composition exhibits reduced antigenicity compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate.

1. Delgado Would Not Have Suggested The Claimed Invention

Delgado *et al.* relates to the activation and coupling of mPEG to GM-CSF, consequently producing a conjugate in which the mPEG has a methoxyl group, not a

hydroxyl group, at the distal terminus of the coupled PEG. *See* the Saifer Declaration at paragraph 13.

Therefore, Delgado fails to disclose a composition in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate. *See id.* Delgado also fails to disclose that the conjugate in such a composition would have exhibited *reduced antigenicity*, compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate. *See id.*

2. Zalipsky Fails To Cure The Deficiencies Of Delgado

Zalipsky relates to the attachment of certain small molecule drugs (not a peptide, protein or glycoprotein) to certain PEG molecules, which are either (a) a PEG with two hydroxyl end groups, *i.e.*, a PEG diol, or (b) a PEG with one methoxyl end group and one hydroxyl end group, *i.e.*, a monomethoxyPEG (also known as "mPEG," which is a type of alkoxyPEG). *See* the Saifer Declaration at paragraph 14 (citing Zalipsky at page 1171, left column, last paragraph to page 1171, right column, first paragraph).

When a PEG diol was coupled to a small molecule drug in Zalipsky, both ends of the diol would have been activated, with the result that a hydroxyl group is not present on at least 95% of the distal polyalkylene glycol termini in the conjugate. *See* the Saifer Declaration at paragraph 15. Therefore, Zalipsky would not have suggested making a conjugate in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate. *See id.*

Activating both ends of a linear PEG diol would have resulted in the crosslinking of two molecules of the drug by PEG. That is, *both ends* of the activated PEG would have been bound covalently to the drug, forming what is called a "dumbbell" structure (Drug-PEG-Drug). *See* the Saifer Declaration at paragraph 16. Therefore, Zalipsky would not have suggested making a conjugate in which at least 95% of said polyalkylene glycol(s) is or are attached to said peptide, protein or glycoprotein at a single site on said polyalkylene glycol(s). *See id.*

In fact, Zalipsky discloses that a free hydroxyl (-OH) group was *not* present, because Zalipsky reported "no absorption for OH at 3300-3500 cm^{-1}." *See* Zalipsky at page 1177, right column, second full paragraph; page 1178, right column, second full paragraph. *See* the Saifer Declaration at paragraph 17.

When a monomethoxyPEG was coupled to a small molecule drug in Zalipsky, the hydroxyl end of the monoalkoxyPEG would have been activated and coupled to the drug, leaving the alkoxy moiety in the resultant alkoxyPEG conjugate exposed. A hydroxyl group would not have been present on at least 95% of the distal polyalkylene glycol termini in such a conjugate. *See* the Saifer Declaration at paragraph 18.

Zalipsky's data also indicate that cross-linking occurred, which is distinct from and not suggestive of the presently claimed composition, since Zalipsky reported that the molar ratio of drug to PEG was twice as high in the conjugates prepared using a PEG diol as the starting material compared with conjugates prepared using mPEG as the starting material (*i.e.*, prior to the activation of the polymer). *See* Zalipsky at page 1178, right column, first paragraph; page 1178, right column, second full paragraph; page 1178, right column, third to last paragraph; page 1179, left column, first full paragraph;

and page 1179, left column, second full paragraph. *See* the Saifer Declaration at paragraph 19.

Finally, Zalipsky fails to disclose a PEG-drug conjugate that exhibits reduced antigenicity compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate. *See* the Saifer Declaration at paragraph 20.

3. Pepinsky Fails To Cure The Deficiencies Of Delgado

The PAG-interferon-beta-1a conjugates disclosed in Pepinsky are alkoxy-PAG-interferon-*beta*-1a conjugates or PEG-aldehyde-interferon-*beta*-1a conjugates. *See* Pepinsky at page 21, lines 13-21; page 22, lines 7-13; page 23, line 7; and page 44, line 7.

Pepinsky fails to disclose a composition in which a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in the conjugate.

Delgado also fails to disclose that the conjugate in the composition would have exhibited *reduced antigenicity* compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate.

4. Even In Combination, The Cited Art Would Not Have Suggested The Claimed Invention

Even in combination, Delgado, Zalipsky and Pepinsky would not have provided the claimed invention. At best, Delgado, Zalipsky and Pepinsky would have provided a composition in which:

(a) *far less than* (not at least) 95% of the polyalkylene glycol(s) is attached to a protein at a single site on the polyalkylene glycol(s);

(b) a hydroxyl group is present on *far less than* (not at least) 95% of the distal polyalkylene glycol termini in the conjugate; and

(c) the conjugate in the composition *does not* exhibit reduced antigenicity, compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate.

Therefore, even if one of ordinary skill in the art would have had a reason to combine the references, Delgado, Zalipsky and Pepinsky -- even in combination -- simply would not have taught or suggested the claimed composition. A *prima facie* case of obviousness has not been established.

B. Reduced Antigenicity Would Not Have Been Predictable From Delgado, Zalipsky And Pepinsky And, In Fact, Is A Surprising Result

Under *KSR*, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." *KSR* at 1739 (emphasis added). Even if Delgado, Zalipsky and Pepinsky were read, incorrectly, to

provide the claimed composition, the combination of Delgado, Zalipsky and Pepinsky would not have yielded predictable results. Specifically, the cited art does not suggest that a composition comprising the claimed conjugate would exhibit *reduced* antigenicity compared to a conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycols of the same size and the same linear or branched structure, in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in the conjugate.

Without being bound by theory, it is believed that the conjugate in the claimed composition exhibits reduced antigenicity because the polyalkylene glycol in the conjugate has a free hydroxyl group, instead of another moiety, such as an alkoxyl group or an aryloxyl group. Indeed, at page 57-58 of the present Specification, in Examples 1-3, and Figures 1-4, Applicants demonstrated that a conjugate in which the polyalkylene glycol has a free hydroxyl group exhibited less antigenicity than a conjugate comprising a methoxyPEG.

This is a truly surprising result, which (a) would not have been predicted from the combination of Delgado, Zalipsky and Pepinsky, and (b) is sufficient to rebut the alleged *prima facie* case of obviousness, even if the *prima facie* case of obviousness were accepted as correct, which it is not.

C. Summary

At least for the reasons discussed above, the claimed composition would have been nonobvious over Delgado, Zalipsky and Pepinsky. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the presently outstanding rejections be reconsidered and withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply are respectfully requested.

Respectfully submitted,

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